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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/SE90/00476 (22) International Filing Date: 3 July 1990 (03.07.90) (30) Priority data: 8902544-9 17 July 1989 (17.07.89) SE (71) Applicant (for all designated States except US): KABIVITRUM AB [SE/SE]; S-112 87 Stockholm (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): KIHLEBERG, Reinhold [SE/SE]; Riddarvägen 37, S-184 51 Österskär (SE). NORRLIND, Björn [SE/SE]; Birkagatan 35, S-113 39 Stockholm (SE). (74) Agents: ONN, Thorsten et al.; AB Stockholms Patentbyrå, Zacco & Bruhn, Box 3129, S-103 62 Stockholm (SE).		(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i> <i>In English translation (filed in Swedish).</i>
(54) Title: A NUTRITIVE COMPOSITION AND A METHOD FOR ITS PREPARATION <div style="text-align: center;"> </div> (57) Abstract <p>The invention relates to a sterile, aqueous nutritive preparation intended for administration to human beings and animals and containing glutamine, and also to a method of producing the preparation. According to the invention, the glutamine, essentially in a water-free state, is sterilized by ionizing radiation, separately from the remaining components of the preparation, and is then combined with the remainder of the preparation. The invention also relates to a packaging device for handling the preparation in its administerable state.</p>		

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A Nutritive Composition and a Method for its Preparation

5 The present invention relates to a sterile, aqueous preparation which is intended for administering nutrients to human beings and animals and containing glutamine, and to a preparation prepared in accordance with the method. The invention also relates to a packaging device for handling such a preparation.

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More specifically, the invention relates to a sterile nutritive composition which contains glutamine together with other nutritive substances, such as amino acids, fats, and then particularly in emulsion form, energy substrates, such as glucose, sugar alcohols and keto acids, vitamins, mineral substances and/or trace elements, and to a method of preparing such a sterile nutritive solution.

20

Background

Observations made in recent years have indicated that glutamine has an important significance when used as a component in nutritive solutions. According to some theories, glutamine, which constitutes the most significant transporter of nitrogen from muscle, has a stimulating effect on the protein synthesis in muscle tissue. Following serious trauma, surgery, sepsis, etc., there occurs a drastic reduction in the free glutamine reserve in skeletal muscle (Vinnars E. Bergström J and Furst P.: Influence of the Postoperative State on the Intracellular Free Amino Acids in Human Muscle Tissue; Annals of Surgery 182:665-671 (1975), and Askanazi J, et al: Muscle and Plasma Amino Acids Follow Injury. Influence of Intercurrent Infection. Ann

Surg. 192:78-85 (1980)). The glutamine is also an essential energy source for the intestinal mucous membrane tissue (Windmueller H.G. Spaeth A E: Identification of Ketone Bodies and Glutamine as the Major Respiratory Fuels in Vivo for Postabsorptive Rat Small Intestine, J Biol. Chem. 253:69-76 (1978)). In total intravenous nutrition, a certain degree of atrophying or wasting occurs in the mucous membrane of the intestines. Experiments on animals have shown that this negative effect can be counteracted, by administering glutamine intravenously. This wasting of the mucous membrane of the intestines observed in conjunction with intravenous nutrition, and also in conjunction with serious trauma can contribute to the passage of bacteria across the intestine wall and into the blood, which can decisively influence the survival chances of the patient concerned. When carrying out experiments on animals whose intestines had been damaged experimentally, glutamine was found to give a longer survival time and a lower mortality rate (Hwang T L, et al: Preservation of Small Bowel Mucosa Using Glutamin-Enriched Parenteralnutrition. Surg. Forum 37:56-58 (1986)).

It is thus desirable to be able to provide a solution or emulsion which contains glutamine together with other nutritive components and which is intended for nutrient administration. One problem, however, is that glutamine solutions cannot be sterilized by autoclaving, since free glutamine in solution is not heat resistant. When a solution which contains glutamine is heated or stored for longer periods at room temperature, the glutamine decomposes to ammonia and pyroglutamic acid. Such substances cannot be accepted in nutritive solutions intended for intravenous administration. This is the reason why no glutamine is

included in the parenteral nutrition amino-acid solutions at present available commercially.

5 Endeavours have been made to overcome this stability problem, by providing glutamine in the form of a derivative, such as dipeptides, for instance, which are more heat resistant and which can therefore be autoclaved together with other amino acids. However, the need to administer the derivative of a compound is not
10 totally satisfactory, since the biological accessibility of the compound can be influenced disadvantageously. The manner in which substances foreign to the body are utilized can also vary considerably from one group of patients to another. Furthermore, it is normally easier
15 to have a substance registered as a drug with the authorities when the substance concerned exists in a non-derivatized form. Furthermore, such glutamine derivatives as dipeptides are considerably more expensive than pure glutamine. The administration of a large
20 quantity of dipeptide can also result in an unnecessarily high supply of some other amino acid, such as glycine or alanine.

The aforesaid drawbacks and disadvantages are eliminated by the present invention, which provides a
25 sterile, aqueous nutritive preparation for administration to human beings and animals and which contains glutamine in a desired mixture with other desirable nutritive additives. Prior to use, the preparation is
30 completely stable when stored and can be readily converted to an administerable or ready-for-use state, even by relatively unskilled persons. Because there is no marked difference between the preparation when in its administerable state and earlier known nutritive
35 preparations, the inventive preparation can be

registered more readily as a drug before the authorities concerned.

5 In accordance with the invention, there is provided a sterile, aqueous nutritive preparation for administration to human beings and animals and containing glutamine, the preparation being characterized in that the glutamine, in a substantially water-free state, has been sterilized by subjecting the preparation to the
10 influence of ionizing radiation, and subsequently combined with the remainder of the preparation. Because the glutamine, in a dry state, has been sterilized by radiation and the remainder of the preparation exists in the form of a sterile solution or emulsion, the ad-
15 ministerable preparation will also be obtained in a sterile state, provided that measures necessary for maintaining sterility are undertaken when combining the sterilized glutamine with the remainder of the preparation. Such measures are well known to one of normal
20 skill in this art.

The present invention also relates to a method of preparing a sterile, nutritive preparation intended for administration to human beings and animals and containing glutamine. The method is characterized in that the
25 glutamine, in a substantially water-free state, is sterilized separately and alone, by subjecting said glutamine to the influence of ionizing radiation, and in that the sterilized glutamine is then combined with
30 the remainder of the preparation.

The present invention also relates to a packaging device for providing an administerable, sterile, aqueous nutritive preparation intended for administration to human beings and animals and containing
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glutamine, said packaging device being characterized in that the device comprises a container constructed from a material which can be penetrated by ionizing radiation and which will not be decomposed by such radiation; in that the container contains a desired quantity of substantially water-free glutamine which has been sterilized by the influence of ionizing radiation; and in that the container is intended to be filled, under sterile conditions, with the remainder of the preparation in solution and/or emulsion form, such as to mix with the glutamine and dissolve the same.

According to one particular embodiment, the inventive packaging device consists of a bag-like container made of plastic foil material which contains the sterilized glutamine and which is provided with known means for delivering and withdrawing a liquid preparation.

Figures 1-3 of the accompanying drawing illustrate embodiments of a packaging device for providing a nutritive preparation in accordance with the invention.

It is previously known that drugs can be sterilized by subjecting the same to the influence of ionizing radiation. It has been found, however, that radiation treatment of all nutritive components in mixture and the subsequent addition of a sterile aqueous phase for producing an administerable preparation, i.e. a preparation which is ready for use, is less suitable, because of the risk incurred by reactions between the various components present when irradiating said components. This risk is avoided when practicing the present invention, since only one of the components of the preparation is irradiated, and then in a water-free state.

Attempts have also been made to achieve sterility of the administerable preparation by sterile filtration techniques. Sterile filtration, however, cannot provide a fully acceptable result from the aspect of sterility, particularly when the preparation shall be administered parenterally, where the requirement of complete sterility is strict. Furthermore, sterile filtration is extremely difficult to carry out in practice, when the preparation contains emulsified fat.

When practicing the present invention, the glutamine and the packaging device in which it is contained are sterilized simultaneously by ionizing radiation, in a manner known per se. The radiation concerned may be X-ray radiation, gamma radiation, electron radiation or some other type of ionizing radiation used conventionally for sterilizing purposes. Gamma radiation emitted from a radioactive nuclide, such as cobalt 60, is often used, as are also high energy electrons from accelerators. The radiation dosage applied for sterilizing the glutamine and its container is conventional and can be readily established by the skilled person on the basis of simple routine experiments, while taking into consideration such factors as the geometric configuration of the irradiated packaging device, the material from which it is made, temperature and like parameters. The radiation dosage applied is normally from 1 to 60 kGy, and then preferably 8-25 kGy.

Those components of the administerable, nutritive preparation additional to the glutamine are conventional and well known to the skilled person. Thus, the preparation can contain further amino acids, essential and non-essential, carbohydrates, such as different sugar types, for instance glucose, fructose and/or

maltose, sugar alcohols, such as sorbitol and xylitol, or keto acids, optionally in the form of salts or esters, water-soluble and/or fat-soluble vitamins, minerals, and/or trace elements. An important nutrient is also fat in an emulsified form. The components included in the preparation and the quantities in which these components are present is determined by the quantity and composition of the nutrient to be administered.

10

The preparation is produced by mixing the ingoing components, in solid, dissolved or emulsified form, with a water phase under sterile conditions, and then incorporating the radiation-sterilized glutamine in the mixture. Because the glutamine is sensitive to heat, incorporation of the glutamine in said mixture should not be effected at too high a temperature, and then preferably not at a temperature above room temperature. It has been found less suitable to first mix all components in a dry state and then add the water phase, since this requires a higher temperature and/or a longer time period in order to achieve complete dissolution.

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When producing the administerable preparation, it has been found particularly advantageous to either add to the sterilized, substantially water-free glutamine the remaining components of the preparation in a dissolved and/or emulsified form, preferably in a packaging device constructed in accordance with the invention, or alternatively by adding the sterilized, essentially water-free glutamine to the solution or emulsion of the remaining preparation components.

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The administerable preparation containing dissolved

glutamine should not be exposed to high temperatures, since the glutamine will then decompose, as explained in the foregoing. Marked decomposition of the glutamine also occurs when storing the preparation at room temperature. The preparation remains relatively stable, however, under cold conditions, and can be stored in a refrigerator for several months without being impaired to any serious extent.

The inventive preparation is particularly suited for parenteral nutritive administration, particularly intravenous administration, to patients who are unable to take-in food in the normal manner, due to injury or illness. High demands are placed on complete sterility of the preparation in cases such as these. The preparation, however, can also be taken orally, either normally or with the aid of a stomach tube.

An inventive packaging device for providing an administerable, sterile nutritive preparation containing glutamine can be constructed in different ways. One suitable embodiment of the inventive packaging device comprises a bag-like container made of plastic foil material and containing the sterilized glutamine. In this case, the packaging device is provided with ports or other known devices through which liquid preparations can be introduced into and removed from the packaging device under sterile conditions. Packaging devices of this kind are known to the art, and it is also known to sterilize empty packaging devices of this kind by ionizing radiation. According to the present invention, a desired quantity of essentially water-free glutamine is introduced into the packaging device, which is then sealed and sterilized by radiation together with its glutamine content. Subsequent to this

sterilizing process, the packaging device and the sterilized glutamine contained therein can be stored for a considerable length of time, before preparing the administerable or ready-for-use preparation.

5

The inventive packaging device can also be configured in various ways, for the production of the administerable preparation. In its simplest form, the inventive packaging device comprises only one single space in which the sterilized glutamine is located and to which the remaining components of the preparation are introduced, in a dissolved or emulsified state.

10

This packaging device configuration is illustrated in Figure 1 of the accompanying drawing. This Figure illustrates a packaging device 1 having an internal container space 2, in which the dry and sterile glutamine 3 is located. The packaging device includes an inlet 4 provided with a closure device 5, through which the remaining components of the preparation are introduced, and an outlet 6 having a closure device 7, through which the administerable preparation is taken from the packaging device. The closure devices 5 and 7 may be configured in different ways. In its simplest and preferred form, in which the packaging device has the form of a plastic-foil bag, the closure devices may simply consist of seam welds formed in the plastic material. When wishing to introduce preparation components into the packaging device, the inlet can be simply cut off beneath the seam weld, so as to permit entry to the space 2, or the preparation components can be introduced into the space 2 with the aid of a cannula, which is inserted through the wall of the packaging device. Removal of administerable preparation can be effected in a similar manner, by cutting open the

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outlet 6, or with the aid of a cannula inserted through the packaging device wall close to the outlet 6. Introduction and withdrawal with the aid of a cannula has the advantage of ensuring complete sterility of the packaging device content more readily, both before and after preparing the administerable preparation.

The closure devices 5 and 7, however, may also have the form of known valve devices incorporated in pipes.

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According to another embodiment, the packaging device may be divided into two spaces, with the glutamine located in one of said spaces. This embodiment is illustrated in Figure 2. In this case, the packaging device 10 is divided into two spaces 11 and 12 which are separated by a partition 13. The partition 13 has formed therein a passageway 14, in which a filter 15 may optionally be incorporated. This filter, for instance, may be a sterile filter. The glutamine 16 is present in a dry and sterile state in the one space 11, and this space may also be provided with an inlet 17 for the introduction of preparation components. The other space is provided with an outlet 18 for the withdrawal of administerable preparation, and optionally also with a further inlet 19 through which additional preparation components can be introduced into the device. The two inlets 17 and 19 and the outlet 18 are also provided with suitable closure devices, as described with reference to the earlier embodiment. These closure devices have not been shown, for the sake of clarity.

When preparing the administerable preparation, the water phase is introduced through the inlet 17 to the

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space 11 containing the glutamine 16, optionally together with dissolved and/or emulsified components, so that the glutamine 16 is dissolved. The glutamine solution with the optionally introduced further components, then flows through the passageway 14 and through the filter 15, when present, to the space 12. Additional components may optionally be introduced into said space, through the inlet 19, and the administerable preparation withdrawn through the outlet 18. Thus, it is not necessary to mix all of the remaining preparation components immediately with the dry glutamine and dissolve said glutamine, but that dissolution of the glutamine can be effected with solely a part of said components. The remaining components of the preparation are then added to the glutamine solution previously prepared.

In accordance with one variant of this second embodiment of the inventive packaging device, the first space may include a column-like structure, in which the glutamine is held. This variant is illustrated in Figure 3, in which corresponding parts of the packaging device are identified with the same reference signs as those used in Figure 2. In this case of the Figure 3 embodiment, the first space 11 has a column-like configuration, in which the dry and sterile glutamine 16 is located. Mounted between the first space 11 and the second space 12 is a passageway or conduit 14, in which a filter 15 may be mounted, for instance a sterile filter. The glutamine solution is collected in the second space 12 and is admixed optionally with further preparation components, entering through the supply line 19, prior to withdrawing the administerable preparation through the outlet 18. Although not shown in the Figure, the inlet and outlet lines are provided

with appropriate closure devices, in a manner similar to the earlier described embodiments.

5 The embodiment illustrated in Figure 3 has the advantage of enabling dissolution of the glutamine to take place under gentler conditions when the water phase is added.

10 All embodiments require the glutamine, enclosed in a dry state in the sealed packaging device, to have been sterilized by ionizing radiation prior to preparing the administerable preparation. Since the dry glutamine has relatively good stability, the glutamine can be stored over a considerable period of time between steriliza-
15 tion and production of the administerable preparation. Complete sterility of the glutamine will be maintained during the whole of this storage period, provided that the packaging device remains fully sealed.

20 It is essential that the inventive packaging device is constructed from a material which will not decompose or emit deleterious reaction products when subjected to the influence of ionizing radiation in the dosages used for sterilization purposes. For instance, different
25 known plastic foil materials can be used. The foil materials used will also preferably be not-readily permeable to gases. Such foil materials may be homogeneous or in laminate form, and several types of material which satisfy these requirements are known to the art.
30 It is also important that the packaging device is constructed in detail in a manner which will permit the introduction of the liquid phase, the dissolution of the glutamine and the withdrawal of the administerable
35 conditions. Liquid packaging devices of such designs

ar also known to the art.

5 The present invention provides a sterile, aqueous preparation which contains glutamine and which is intended for administration to human beings and animals. This has not earlier been possible to achieve. The method of preparing the administerable preparation is also simple and the major part of the method is based on known techniques. Empty bag-like packaging
10 devices are already sterilized by ionizing radiation in present times, and it is technically simple to place dry glutamine in the packaging devices prior to irradiation. Conventional methods and also conventional apparatus are found for subsequently introducing the
15 remaining nutritive components, in a dissolved or emulsified state into the packaging devices at desired times.

Claims

1. A sterile, aqueous nutritive preparation intended for administration to human beings and animals and containing glutamine, characterized in that the glutamine, in a substantially water-free state, has first been sterilized by subjecting the glutamine to the effect of ionizing radiation, and thereafter combined with the remainder of the preparation.
2. A preparation according to Claim 1, characterized in that it contains further amino acids in addition to glutamine, fat in emulsified form, carbohydrates, vitamins, minerals and/or trace elements.
3. A preparation according to Claim 1 or 2, characterized in that combining of the glutamine with the remainder of the preparation has been effected by adding said remainder, in a dissolved and/or emulsified form, to the sterilized, substantially water-free glutamine.
4. A preparation according to any one of Claims 1-3, characterized in that sterilization has been effected with a radiation dosage of 1-60 kGy, preferably 8-25 kGy.
5. A method of producing a sterile, aqueous nutritive preparation intended for administration to human beings and animals and containing glutamine, characterized in that the glutamine, in a substantially water-free state, is sterilized separately and alone, by subjecting the glutamine to the influence

of ionizing radiation, whereafter the sterilized glutamine is combined with the remainder of the preparation.

5 6. A method according to Claim 5, c h a r a c -
t e r i z e d in that said sterilization is effective
with a radiation dosage of 1-60 kGy, preferably
8-25 kGy.

10 7. A method according to Claim 5 or 6, c h a r -
a c t e r i z e d in that the glutamine is combined
with the preparation by adding the remaining prepara-
tion components, in a dissolved or emulsified state, to
the sterilized, substantially water-free glutamine.

15 8. A method according to Claim 5 or 6, c h a r -
a c t e r i z e d in that the glutamine is combined
with the preparation, by adding the sterilized, sub-
stantially water-free glutamine to a solution or emul-
sion of the remaining components of the preparation.

20 9. A packaging device for providing administerable,
sterile aqueous, nutritive preparation intended for
administration to human beings and animals and contain-
ing glutamine, c h a r a c t e r i z e d in that the
25 packaging device comprises a container made of a mater-
ial which is permeable to ionizing radiation but which
will not be decomposed by said radiation, in that the
container contains a desired quantity of substantially
water-free glutamine which has been sterilized through
30 the influence of ionizing radiation, and in that the
container is intended to be filled, under sterile
conditions, with the remainder of the preparation, in
solution and/or emulsion form, and mixed with the
glutamine such as to dissolve said glutamine.

10. A packaging device according to Claim 9,
c h a r a c t e r i z e d in that it comprises a bag-
like container made of plastic-like foil material and
5 containing the sterilized glutamine, and in that the
packaging device is provided with known devices for the
introduction and removal of liquid preparation.

10 11. A packaging device according to Claim 9 or 10,
c h a r a c t e r i z e d in that the container is
divided into two spaces which are mutually connected,
optionally through a filter; in that the glutamine is
located in one of said spaces; in that the spaces are
15 so disposed that a part of the preparation, or the
remainder of the preparation, in solution and/or emul-
sion form is introduced into the space in which the
glutamine is located and dissolves said glutamine,
whereafter the resultant preparation is caused to flow
20 to the second space, from which said preparation is
withdrawn.

12. A packaging device according to Claim 11,
c h a r a c t e r i z e d in that the space in which
the glutamine is located has a column-like con-
25 figuration and is so constructed that a part of the
preparation, or the remainder of the preparation, is
introduced into the column with the glutamine and
dissolves said glutamine, and is thereafter caused to
flow to the second space.

30 13. A packaging device according to Claim 11 or 12,
c h a r a c t e r i z e d in that the second space is
also provided with means for introducing and with-
drawing preparation components.

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FIG.1

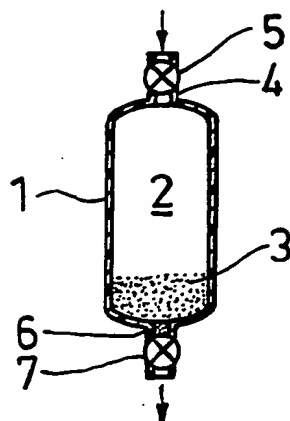


FIG.2

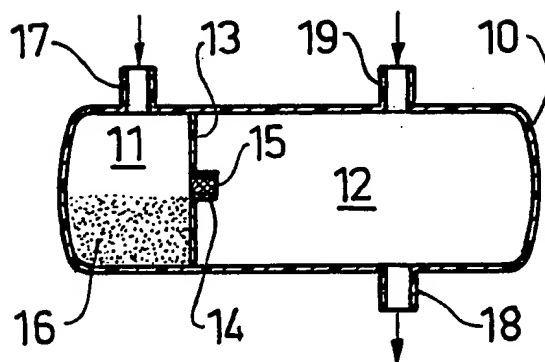
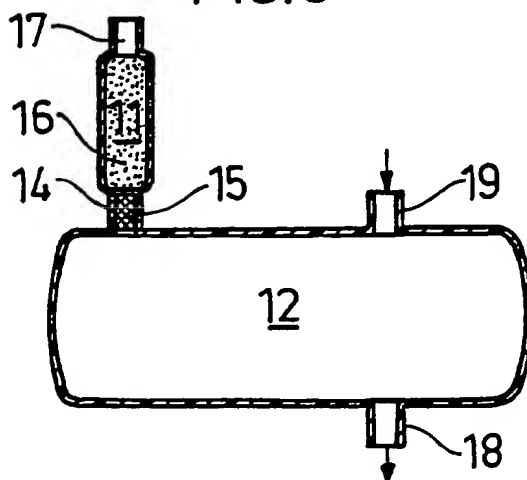


FIG.3



INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 90/00476

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: A 61 K 31/195, A 61 L 2/08, A 61 J 1/00														
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border: 1px solid black; text-align: left;">Classification System</th> <th style="border: 1px solid black; text-align: left;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">IPC5</td> <td style="border: 1px solid black; padding: 5px;">A 61 K; A 61 L; A 61 J; B 65 B</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div> <p style="padding: 5px;">SE,DK,FI,NO classes as above</p>			Classification System	Classification Symbols	IPC5	A 61 K; A 61 L; A 61 J; B 65 B								
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border: 1px solid black; text-align: left;">Category *</th> <th style="width: 60%; border: 1px solid black; text-align: left;">Citation of Document,¹¹ with Indication, where appropriate, of the relevant passages¹²</th> <th style="width: 30%; border: 1px solid black; text-align: left;">Relevant to Claim No.¹³</th> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top;">Y</td> <td style="border: 1px solid black; padding: 5px;"> WO, A1, 8701589 (BRIGHAM AND WOMEN'S HOSPITAL) 26 March 1987, see esp. page 11, lines 19-30 and page 12, line 26 - page 14, line 18 -- </td> <td style="border: 1px solid black; text-align: center; vertical-align: top;">1-13</td> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top;">Y</td> <td style="border: 1px solid black; padding: 5px;"> WO, A1, 8903688 (AB ERIK VINNARS ET AL.) 5 May 1989, see esp. page 4, line 23 - page 5, line 12; page 7, line 7 - page 8, line 10 and claim 7 -- </td> <td style="border: 1px solid black; text-align: center; vertical-align: top;">1-13</td> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top;">Y</td> <td style="border: 1px solid black; padding: 5px;"> GB, A, 657295 (ELECTRONIZED CHEMICALS CORPORATION) 19 September 1951, see esp. page 3, lines 38-96 and claim 2 -- </td> <td style="border: 1px solid black; text-align: center; vertical-align: top;">1-13</td> </tr> </table>			Category *	Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	Y	WO, A1, 8701589 (BRIGHAM AND WOMEN'S HOSPITAL) 26 March 1987, see esp. page 11, lines 19-30 and page 12, line 26 - page 14, line 18 --	1-13	Y	WO, A1, 8903688 (AB ERIK VINNARS ET AL.) 5 May 1989, see esp. page 4, line 23 - page 5, line 12; page 7, line 7 - page 8, line 10 and claim 7 --	1-13	Y	GB, A, 657295 (ELECTRONIZED CHEMICALS CORPORATION) 19 September 1951, see esp. page 3, lines 38-96 and claim 2 --	1-13
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Y	WO, A1, 8903688 (AB ERIK VINNARS ET AL.) 5 May 1989, see esp. page 4, line 23 - page 5, line 12; page 7, line 7 - page 8, line 10 and claim 7 --	1-13												
Y	GB, A, 657295 (ELECTRONIZED CHEMICALS CORPORATION) 19 September 1951, see esp. page 3, lines 38-96 and claim 2 --	1-13												
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search 16th October 1990 </td> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report 1990 -10- 19 </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;"> International Searching Authority SWEDISH PATENT OFFICE </td> <td style="border: 1px solid black; padding: 5px;"> Signature of Authorized Officer <i>Gunilla Claesson</i> Gunilla Claesson </td> </tr> </table>			Date of the Actual Completion of the International Search 16th October 1990	Date of Mailing of this International Search Report 1990 -10- 19	International Searching Authority SWEDISH PATENT OFFICE	Signature of Authorized Officer <i>Gunilla Claesson</i> Gunilla Claesson								
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International Searching Authority SWEDISH PATENT OFFICE	Signature of Authorized Officer <i>Gunilla Claesson</i> Gunilla Claesson													

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	J.E. Hoover, "Remington's Pharmaceutical Sciences", 15.Ed., 1975, Mack Publishing Co. (Easton, Pennsylvania), see pages 1397-1400 and 1482-1483 --	1-13
X	EP, A2, 0116362 (MILLIPORE CORPORATION) 22 August 1984, see esp. page 2, line 2 - page 3, line 28 and Figure 1	9-13
Y	--	9-13
X	EP, A2, 0132632 (ABBOTT LABORATORIES) 13 February 1985, see esp. page 9, line 30 - page 10, line 11 and the Figures	9-13
Y	-- -----	9-13

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 90/00476**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on **90-09-27**.
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO-A1- 8701589	87-03-26	AU-B-	599335	90-07-19
		AU-D-	6337886	87-04-07
		EP-A-	0238553	87-09-30
		JP-T-	63501214	88-05-12
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		EP-A-	0318446	89-05-31

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